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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LONG, SCOTT	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,068	LEVY ET AL.	
	Examiner	Art Unit	
	Scott D. Long	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34, 41-45, 52-56, 59, and 66-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,41-45,52-56,59 and 66-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner of record has changed. Please direct all further correspondence to Scott Long whose phone number is 571-272-9048.

The examiner acknowledges receipt of Request for RCE (filed 8/7/2007), and Claim Amendments and Applicant's Remarks (filed 5/14/2007)

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 14, 2007 has been entered.

Claim Status

Claims 34 and 67 are amended. Claims 71-73 are newly submitted. Claim 1-33, 35-40, 46-51, 53, 57-58, and 60-65 are cancelled. Claims 34, 41-45, 52-56, 59, and 66-70 are under current examination.

Priority

This application claims benefit from as DIV of 09/851,327 (filed 05/09/2001; issued as PAT 6,919,208) which claims benefit of 60/206,143 (filed 05/22/2000). The instant application has been granted the benefit date, 22 May 2000, from the application 60/206,143.

As claim 53 has been canceled in the admitted claim amendments, the previous examiner's request for amendment to the specification to clarify the status of the application (see *Priority* sections of Actions filed 4/21/2006 and 2/7/2007) is hereby withdrawn. The current examiner views the application as complying with 35 USC 119(e) or 35 USC 120, 121, or 365(c) and benefit, as described above, has been granted.

Oath/Declaration

The applicant has canceled the claims that the previous examiner believed were cause for objecting to the oath under MPEP 602. Therefore, the issue is moot and the current examiner hereby withdraws the objection.

Specification

The objection to the specification is hereby withdrawn. The examiner believes that cancellation of claim 53, has satisfied the objection of the previous examiner.

Response to Arguments - Claim Objections

The applicant's remarks and claim amendments (filed 5/14/2007) with respect to claim 60 have been fully considered and are persuasive.

The examiner believes that cancellation of claim 60, has satisfied the objection of the previous examiner. The objection to claim 60 is hereby withdrawn.

Response to Arguments - Claim Rejections 35 USC § 112

The applicant's remarks (5/14/2007 and 8/7/2007) and claim amendments (filed 5/14/2007) with respect to claims 68-70 have been fully considered but are not persuasive.

The current examiner cannot withdraw the new matter rejection of claims 68-70 because he concludes that the basis of the previous examiner's rejection of claims 68-70 was not addressed through amendment of claims 68-70. Rather, the applicant has chosen to address the pending rejection by adding new claims 71-73. The newly submitted claims do not overcome the issues of claims 68-70.

While the applicant nearly admitted that all methods of denaturing collagen are obvious to one skilled in the art, the applicant did not actually so state. Rather, the applicant states, "While the specific example teaches that the collage was boiled in acidic conditions for one hour, the length of time can be varied be (*sic*) a skilled artisan so long as denaturation of the collagen occurs" (Remarks, page 2, 8/7/2007). In

addition, the applicant, in trying to overcome the previous examiner's assertion of new matter states, "the disclosure at page 27, lines 13-16 that the Examples should be construed to encompass any and all variations" (Remarks, filed 8/7/2007, page 3, parag.1). The specification states, "these Examples...should be construed to encompass any and all variations which become evident as a result of the teachings provided herein" (page 27, lines 13-16). The current examiner does not understand how the discussion over denatured collagen has degenerated into such arguments, where the method of making a claimed reagent such as denatured collagen, has become the basis for such intense debate. A clear statement by the applicant that the method of collagen denaturation is obvious to a skilled artisan would resolve the issue of new matter for the current examiner. Such an admission, would make moot all disagreements regarding the patentability of particular limitations drawn to how the collagen is denatured. The current examiner could then easily withdraw the new matter rejection and both applicant and examiner can focus on truly distinguishing features of the applicant's invention.

Therefore, the examiner hereby maintains the rejection of claims 68-70 under 35 USC 112, 1st paragraph (written description-new matter) for the reasons of record and the discussion above.

The applicant's remarks and claim amendments (filed 5/14/2007) with respect to claims 57-58 have been fully considered and are persuasive. Cancellation of claim 57-

58 have made the rejection moot and therefore the examiner hereby withdraws the rejection of claims 57-58 under 35 USC 112, 1st paragraph (lack of enablement).

The applicant's remarks and claim amendments (filed 5/14/2007) with respect to claims 34 and 41-44 have been fully considered and are persuasive. The amendment of claim 34 to recite "*in vitro*" has overcome the basis for the 35 USC 112, 1st paragraph (enablement) rejection based on *in vivo* embodiments. Amendments to claim 34 has made the rejection moot and therefore the examiner hereby withdraws the rejection of claims 34 and 41-44 under 35 USC 112, 1st paragraph (lack of enablement).

Response to Arguments - Claim Rejections 35 USC § 102

Claims 34, 41-45, 52, 55, 59, and 66 remain rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Arrow et al., US 5,849,902 (issued 15 December 1998) for the reasons of record set forth in the Office action of 4/21/06 and 2/7/2007.

Claims 34, 41, 44-45, 52, 54-56, 59, and 66 remain rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Isner, US 5,652,225 (issued 29 July 1997) for the reasons of record set forth in the Office action of 4/21/06 and 2/7/2007.

Claims 34, 41, 44, 45, 52, 54, 56, 59, and 66 remain rejected under 35 U.S.C. 102(a) & (e) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Truong et al., US 6,025,337 (issued 15 February 2000) for the reasons of record set forth in the Office action of 4/21/06 and 2/7/2007.

All of the references teach the limitation of newly amended claim 34, "*in vitro*" methods.

The applicant also argues that "amended claim 67, which depends from claim 34, recites the additional step of comparing the expression of the heterologous protein or polypeptide in the presence and absence of denatured collagen to determine the enhancement of the efficiency of delivering the nucleic acid molecule to the cell. Figure 5 of Truong et al. shows the results of transfection studies that include a control sample which comprises only cDNA. (See also paragraph 27 for further description of these results). According to Truong et al., the free cDNA showed no evidence of transfection, when compared to microspheres with cDNA. The other references also present data from controlled experiments.

Therefore, the examiner hereby maintains the rejection of claims under 35 USC 102 as anticipated by or under 35 USC 103 as obvious over the Arrow or Isner or Truong.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The claimed invention is directed to an *in vitro* method of enhancing the efficiency of delivery of a nucleic acid encoding a heterologous protein or polypeptide to a cell, said method comprising a) providing to said cell *in vitro* with at least one agent capable of enhancing the cytoskeletal permissiveness of said cell for transfection in an mount effective to enhance said cytoskeletal permissiveness, and b) providing to said cell *in vitro* with said nucleic acid encoding said heterologous protein or polypeptide for

the transfection of said cell, whereby the efficiency of delivery of said nucleic acid to said cell is enhanced.

Claims 34, 41-45, 52, 54-56, 59, and 66-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arrow et al., US 5,849,902 (issued 15 December 1998) in view of Isner, US 5,652,225 (issued 29 July 1997) and further in view of Truong et al., US 6,025,337 (issued 15 February 2000) and further in view of Jones et al. (Journal of Cell Science. 1999, vol.112: 435-445).

Arrow (col. 6-7) describes a method of transfecting HeLa cells with a plasmid encoding a heterologous protein or polypeptide comprising culturing the cells on a plate coated with denatured collagen (gelatin) then exposing the cells to a liposomal preparation comprising Lipofectin™, which is a vehicle suitable for pharmaceutical delivery, comprising the plasmid. This is basically the same general method as described in instant example 1. The final transfection mixture is a composition comprising the denatured collagen and the nucleic acid. Given that the cell is in contact with the gelatin coating before, during, and after exposure to the nucleic acid, the method meets the limitations of claims 41-43. Claim 53 recites an intended use that does not materially affect the composition. With respect to the kit (claim 59), instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (Fed. Cir. 1983). The reference does not disclose cellular processes caused by exposure of the cell to denatured collagen (gelatin). However, the instant specification teaches that denatured collagen causes an increase in cytoskeletal

permissiveness. Therefore absent evidence to the contrary this is an inherent property of contacting a mammalian cell with denatured collagen as in the prior art method.

Isner discloses a method for gene therapy comprising delivery of a vector comprising a nucleic acid encoding a heterologous polypeptide or protein to arterial endothelium and smooth muscle using a vascular balloon catheter coated with a hydrogel, such as denatured collagen (gelatin), containing the vector. The vector may be naked plasmid DNA, an adenovirus or cationic liposome. See entire document, especially, col. 1-3, 4-9, claims 1-6. With respect to the kit (claim 59), instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (Fed. Cir. 1983). The reference does not disclose cellular processes caused by exposure of the cell to denatured collagen (gelatin). However, the instant specification teaches that denatured collagen causes an increase in cytoskeletal permissiveness. Therefore absent evidence to the contrary this is an inherent property of contacting a mammalian cell with denatured collagen as in the prior art method.

Truong describes a composition of microparticles comprising denatured collagen (gelatin) and a plasmid vector comprising nucleic acid encoding a heterologous protein or polypeptide, and a method of using same to transfect mammalian cells *in vitro* and *in vivo*. Such microparticles are characterized by controlled release of their constituents. See entire reference, for example col. 2 and claims 1-16 and 27-37. With respect to the kit (claim 59), instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those

materials. *In re Gulack*, 217 USPQ 401 (Fed. Cir. 1983). The reference does not disclose cellular processes caused by exposure of the cell to denatured collagen (gelatin). However, the instant specification teaches that denatured collagen causes an increase in cytoskeletal permissiveness. Therefore absent evidence to the contrary this is an inherent property of contacting a mammalian cell with denatured collagen as in the prior art method. In addition, Figure 5 of Truong et al. shows the results of transfection studies that include a control sample which comprises only cDNA. (See also paragraph 27 for further description of these results). According to Truong et al., the free cDNA showed no evidence of transfection, when compared to microspheres with cDNA.

Arrow and Isner and Truong do not particularly teach the limitations of claims 68-73, directed to the method of claim 34 (or 45 or 59), wherein said denatured collagen or a peptide of denatured collagen is denatured at 100°C at pH 3 and wherein said denaturation is performed for one hour.

Jones is the only prior art that the Examiner is aware of that teaches denaturing collagen near pH 3 at 100°C or near to using 0.17% acetic acid (28mM) at 100°C. Jones used 20 mM acetic acid, which would yield a pH of about pH 3.25. The Examiner found a wide variety of different conditions in use to denature collagen to make gelatin that result in gelatin of differing physical properties, but no evidence that the particular conditions recited in claims 68-70 (or in Jones) were commonly (or even uncommonly) used. Consequently, there is no evidence of record that suggests preparing the denatured collagen for use in the methods or compositions of Arrow, Isner, or Truong

under the conditions recited in claims 68-70, or that the gelatin would not be physically identical to that prepared by other prior art methods.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to employ a method of enhanced transfection comprising nucleic acids and a denatured collagen, wherein the method used to denature collagen is by any means known in the art.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute denatured collagen made by any known method for the denatured collage described in Arrow, Isner, or Truong.

The person of ordinary skill in the art would have been motivated to substitute one known, equivalent element for another to obtain predictable results. The claimed methods would have been obvious because the substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. In the instant case, it would have been obvious to substitute a denatured collagen made by boiling in acidic conditions for an hour for any collagen made by other means in the methods of Arrow, Isner, or Truong.

Therefore the method as taught by Arrow in view of Isner and further in view of Truong and further in view of Jones would have been *prima facie* obvious over the method of the instant application.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JLE